Cholangiocarcinoma: Epidemiology and Imaging-Based Review

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ABSTRACT

Cholangiocarcinoma (CCA) is a rare cancer of the bile duct epithelium, and in the last few decades its incidence rate has been increasing. It is associated with a high mortality rate due to late diagnosis and its aggressive nature. Many risk factors have been identified; some are more common in certain regions than others. CCA can be classified according to its anatomical location or macroscopic growth pattern, the latter being most helpful for imaging interpretation. Clinical features can vary from obstructive-like symptoms to nonspecific symptoms, such as weight loss and malaise. Imaging, specifically MRI/MRCP, is crucial in diagnosing CCA, staging, and treatment planning. Surgery with chemotherapy is the mainstay treatment option, and other palliative treatment options exist for those who have unresectable disease.

KEYWORDS: Cholangiocarcinoma, Imaging, MRI, MRCP, CT, Ultrasound, Biliary Tract

INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common form of primary liver neoplasm but makes up less than 2% of all cancers.[1,2] CCAs represent a diverse set of aggressive malignancies arising from different locations of the biliary tract, excluding those deriving from the gallbladder or ampulla of Vater. The development of CCA is poorly understood, but a complex interaction between genetics and multiple risk factors is suggested.

Trending the incidence rate of CCA has proved difficult due to misclassification of CCAs and changes in the International Classification of Diseases for Oncology (ICD-O) coding over time. However, in the past few decades a global rise in CCA incidence has been observed.[3] Geographically, incidence is highest in Eastern Asia countries such as Thailand, where age-adjusted incidence rates are as high as 85 per 100,000 compared to the reported rate of between 0.8 to 2 per 100,000 in the Western world.[3,4]

Diagnosis of CCA depends on clinical suspicion, laboratory tests, and imaging, with surgical resection being the gold standard for treatment. Despite medical advances over the past few decades, prognosis remains poor due to late presentation, high rate of recurrence, and aggressive nature of the tumor. Some studies have reported a five-year survival rate as low as 5%, and up to 75% of patients die within the first year of diagnosis.[5] This review provides a brief overview of CCA, diagnostic steps, treatment options, and associated outcomes.

CHOLANGIOCARCINOMA

CCAs are categorized into three main types based on anatomical location: intrahepatic, extrahepatic, and perihilar. Perihilar CCA is the most prevalent, making up 50–60% of CCA cases, followed by distal CCA (20–30%) and intrahepatic CCA (10–20%).[1,6] CCA can also be classified based on macroscopic growth patterns: mass-forming, intraductal growing, and periductal infiltrating. Mass-forming CCAs are solid intrahepatic tumors discrete from the surrounding liver parenchyma, and they tend to metastasize within the liver. Intraductal growth is mainly confined to the biliary tract lumen and is the least aggressive subtype. The periductal subtype usually involves surrounding portal structures and grows longitudinally, and it can invade neighboring liver parenchyma; however, it is not associated with a solid mass like mass-forming CCAs and has a predilection to metastasize to hilar lymph nodes.[7,8,9] Morphologic descriptions can aid with imaging interpretation and diagnosis.

Intrahepatic cholangiocarcinoma (iCCA) can arise from large intrahepatic ducts peripheral to the left and right hepatic ducts or smaller ducts located within the periphery of the liver parenchyma.[7,10] Morphologically, the mass-forming type makes up about 60%, while intraductal and periductal types comprise 20% of all iCCAs.[11] iCCAs can be fibrotic, an important feature that gives it a characteristic imaging appearance, and in 20% of cases, can cause capsular retraction.[12]

Extrahepatic cholangiocarcinoma (eCCA), an umbrella term for perihilar cholangiocarcinoma (pCCA), also known as Klatskin tumor, and distal cholangiocarcinoma (dCCA), makes up 70–80% of CCA cases. Anatomically, pCCA is located central to the left and right hepatic ducts but peripheral to the cystic duct. These tumors are classified according to the degree of biliary tract involvement (Bismuth-Corlette classification) and can be labeled as Type 1, Type 2, Type 3A/3B, and Type 4. Meanwhile, dCCA is central to the cystic duct and involves the common bile duct.[13]

EPIDEMIOLOGY

CCA usually presents between the fifth and seventh decade of life, with men being more affected than women. Patients with increased risk factors, those with primary sclerosing cholangitis (PSC) or congenital abnormality of the biliary tree, can present decades earlier compared to those with average risk.[14] CCA is uncommon in the Western world, with incidence rates less than 2 per 100,000, but incidence can increase by 40-fold in endemic areas, such as Thailand.[4] Recently, increasing incidence rates have been reported globally.[3] In the United States, a sharp rise in iCCA compared to eCCA has also been noted, with a 350% increase in iCCA incidence rate compared to a 20% increase with eCCA. This rise in CCA incidence rate has been observed across different races, sexes, and ethnicities.[13,15] Another study looking at a 40-year trend in the incidence of CCA in the United States reports an increase in iCCAs from .44 to 1.18 per 100,000. In contrast, the incidence of eCCAs has been stable from 1973 to 2012.[16] Hispanic patients have a higher incidence rate, 1.22 per 100,000, while African Americans have the lowest incidence rate at 0.3 per 100,000. Specifically, in Rhode Island, incidence rates have also increased in the past decades (**Table 1**).

Risk factors vary based on geographical location. For example, parasites are considered a significant risk factor for developing CCA in East Asian countries, where infections with the liver fluke *Opisthorchis viverrini,* are common. Primary sclerosing cholangitis (PSC) and fibropolycystic liver disease are considered important risk factors for developing CCA in Western countries.[17] Almost 50% of patients develop CCA within one year of PSC diagnosis.[18] Thorotrast, a now-banned contrast agent, is also strongly associated with CCA. The literature describes many important risk factors involving the pathogenesis of CCAs. These risk factors, however, only account for a minority of CCA cases and vary in global distribution.[1,19,20]

CLINICAL FEATURES

The clinical presentation of patients with CCA can differ depending on the subtype of CCA. Patients with eCCA typically present with obstructive symptoms, such as jaundice, due to the anatomical location of eCCA. Most patients with iCCA are asymptomatic or have nonspecific signs, with about 12-30% of cases being found incidentally at an advanced stage of disease.[21] Initial workup includes obtaining a right upper quadrant ultrasound and blood test for bilirubin levels, serum aminotransferases (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) levels. Additional serological tests, including CA 19-9 and CEA, can also aid in diagnosing CCA. CA 19-9 and CEA levels require careful interpretation as both can be elevated in many benign conditions.[22] Alpha-fetoprotein (AFP), specific for hepatocellular carcinoma (HCC), can help distinguish between iCCA and HCC since both present as solid liver tumors and share similar risk factors.[23]

IMAGING FEATURES

The diagnostic approach in symptomatic patients depends on suspicion of CCA, patient history of PSC, and suspected CCA type. Patients with obstructive symptoms or right upper quadrant pain usually undergo transabdominal ultrasound since it can quickly confirm dilatation and obstruction and help rule out benign causes such as gallstones.[24] If suspicion for CCA remains high, additional imaging with cross-sectional imaging can be considered. Cross-sectional imaging is crucial for diagnosing CCA, as it assists in characterizing tumors, detecting metastases, and assessing vasculature involvement. These aspects are integral for staging and treating CCA effectively. It is also crucial to consider other diseases, specifically HCC and metastases to the liver.

Transabdominal Ultrasound

Transabdominal ultrasound (TAUS) has a high sensitivity for identifying and localizing the site of obstruction. A study with 429 patients examining the diagnostic accuracy of TAUS found it to have 89% and 94% sensitivity for identifying and localizing the site of obstruction, respectively.[25] Imaging findings can vary depending on the type of CCA. iCCA tends to present as a large mass with ill-defined and irregular borders, with varying echogenicity (**Figure 1**). Depending on the tumor's location, eCCA may only cause intrahepatic dilation or dilation of both intrahepatic and extrahepatic ducts. Dilation of the biliary duct greater than 6 mm, in the absence of gallstones, is considered to be due to obstructive lesions in an average-risk patient.[25] Patients with PSC may not show bile duct dilatation on TAUS, but worsening of duct dilation and the presence of dominant stricture makes CCA highly likely.[26] The differential for a hepatic mass includes HCC and liver metastases. On ultrasound, the presence of solid nodule(s) exhibiting diverse

Table 1. Demographics and age-adjusted incidence rate of cholangiocarcinoma (ICD-O-3 8160/3) in RI (1995–2019)

Demographics	Mean Age (years)	Male (%)	White(%)		
	67.89 ± 12.73	50.66	89.6		
Incidence	1995–1999	2000–2004	2005–2009	2010–2014	2015–2019
Age-adjusted incidence rate, per 100,000 individuals	1.10	0.85	1.27	1.84	2.18

Figure 1. Transverse ultrasound images of the right hepatic lobe demonstrate a solid irregular hypoechoic mass (white arrow), measuring 3.71 x 3.42 x 3.23 cm.

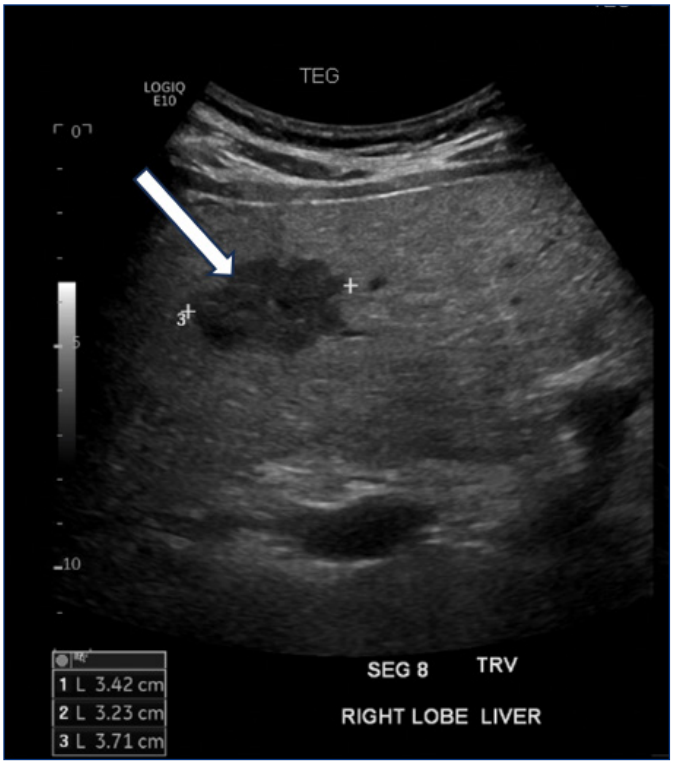
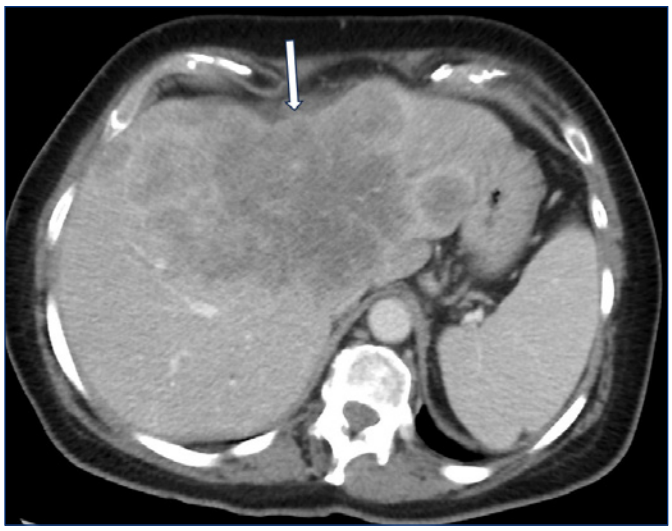


Figure 2. Axial CT image demonstrates numerous hypodense masses in the liver, with a dominant mass with indistinct margins centered in hepatic segment 4. Capsular retraction can also be seen adjacent to the mass (white arrow)



echogenicity and homogeneity, along with irregular borders, is indicative of HCC. HCC on contrast-enhanced ultrasound (CEUS) can present with enhancement in the arterial phase due to neovascularity and it's followed by a washout phase during the portal venous phase.[27] Liver metastases have a diverse presentation and ultrasound is rarely used given its limitations.[28]

Computed Tomography

If suspicion for CCA is high, computed tomography (CT) can be considered for initial imaging. It can accurately identify intrahepatic masses and locate obstructions. In its portal venous phase, it can differentiate between benign and malignant causes of intrahepatic strictures.[12,29] iCCAs can present as large non-capsulated hypodense masses with peripheral duct dilation and peripheral enhancement (arterial and venous phases) with late centripetal spread. These hypodense lesions can either be poorly or well-differentiated and can display liver capsular retraction depending on its stromal component (**Figure 2**).[12,30] The rare mixed hepatocellular-cholangiocellular carcinoma (HCC-CCA), a subtype of iCCA, may show imaging patterns distinct from that of HCC and CCA and often requires biopsy for confirmation.[31]

Contrast is necessary for working up CCA, as its different phases can reveal additional information necessary for diagnosis, staging and treatment planning. The arterial phase can reveal important vascular anatomy of the liver and surrounding structures, which is crucial for surgical planning. In the portal venous phase, iCCA shows weak peripheral contrast enhancement with low intratumoral attenuation. The size of the tumor and the presence of satellite nodules can be deduced. In late-phase scan, usually 10 minutes after contrast injection, a peripheral washout with a centripetal spread can be seen. Sometimes, this delayed enhancement may not appear. Taken together, the late-phase scan can give a sneak peek into the makeup of the tumor. Tumors with high fibrosis display late centripetal contrast due to contrast trapping, and tumors with necrosis and/or mucin fail to enhance.[32]

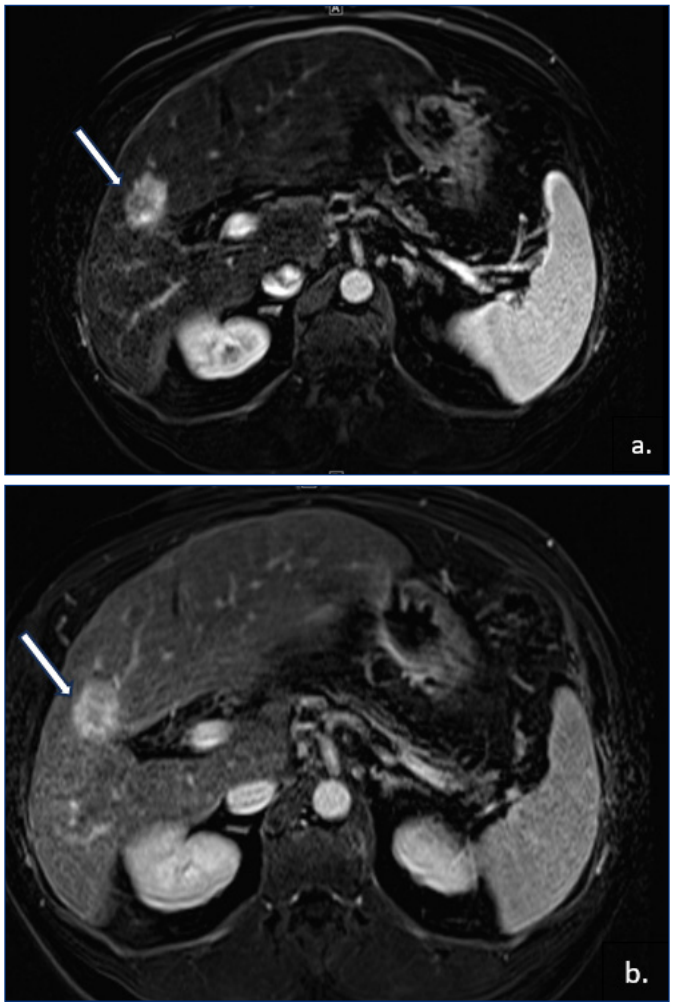
With eCCAs, lesions can be localized based on where ductal dilation is observed. pCCA lesions arise near the perihilar region, and imaging features depend on the degree of bile duct involvement. Bilateral intrahepatic duct dilatation or non-union of the left and right hepatic duct, without gallbladder distension, is suggestive of pCCA. Tumors arising from either left or right hepatic duct can be large, with intrahepatic duct dilation proximal to the tumor and with liver parenchyma infiltration. Dilation of both intrahepatic and extrahepatic ducts with gallbladder distension indicates a centrally located lesion suggestive of dCCA.[1,33] When compared with its main differential consideration, HCC on CT presents as a hypodense or isodense lesion with non-rim arterial phase hyperenhancement followed by rapid washout in the portal venous phase.[34] The other more common differential consideration, liver metastases, tend to be hypovasular and present as a hypodense lesion during the portal venous phase, where the liver parenchyma enhances.[28]

Magnetic Resonance Imaging

Due to its superior soft tissue contrast and ability to provide detailed anatomical information about the biliary tract, magnetic resonance imaging (MRI), in conjunction with magnetic resonance cholangiopancreatography (MRCP), is currently the modality of choice for diagnosing and staging CCA.[35] MRI is crucial for preoperative planning as it can accurately evaluate the extent of the tumor, vascular involvement, and resectability, thus having a significant impact on surgical outcomes.[36] In patients with PSC, MRI/MRCP is utilized for surveillance since the lifetime incidence of CCA is higher than non-PSC patients. In recent years, MRCP has become the imaging of choice over traditional invasive procedures, like endoscopic retrograde cholangiopancreatography (ERCP), for examining the biliary tract. MRCP is purely diagnostic compared to ERCP, which can also be used for therapeutic purposes; however, this is a small trade-off as MRCP has been found to be more effective at identifying obstructive lesions and analyzing the extent of the lesion compared to ERCP.[37]

One study comparing MRI/MRCP to CT with direct cholangiography on the ability to evaluate tumor extent and resectability of bile duct cancer found that MRI/MRCP has a similar diagnostic capability to that of CT, with a diagnostic rate of 90.7% and 87% for lesions involving the secondary biliary confluences and intrapancreatic common bile duct, respectively. CT showed a similar diagnostic rate at 85.1% and 87%, and the difference in the performance between the two was not statistically significant ($p>0.05$).[38] On MRI, mass-forming iCCAs can present as hypointense lesions on T1-weighted imaging or heterogeneously hyperintense with central hypointensity on T2-weighted imaging. Similar to CT, MRI can show initial peripheral enhancement with gradual centripetal spread after contrast injection. Delayed central enhancement, combined with peripheral washout, can give the lesions a targetoid appearance (**Figure 3**).[39] Periductal growth presents with wall thickening at the level of the lesion with peripheral ductal dilation and late-phase contrast enhancement. On contrast-enhanced MRI, mixed HCC-CCA can display irregular shape with sharp rim enhancement in the early dynamic phases without targetoid appearance. This targetoid appearance favors CCA and can help to differentiate it from HCC.[40] Specifically, HCC on MRI presents as a hypointense mass on T1-weighted sequences and a hyperintense mass on T2-weighted sequences, with marked arterial hyperenhancement on the arterial phase followed by portal venous phase washout.[34] Alternatively, metastatic lesions presentation can vary based on the primary cancer, but usually present as hypointense lesions on T1-weighted sequences and hyperintense lesions on T2-weighted sequences, with enhancement. Metastatic lesions do not retain contrast during the hepatobiliary phase when hepatocyte-specific MRI contrast agents such as eovist are used.[28]

Figure 3. [**a**] Axial T1 post-contrast subtraction non-delayed and [**b**] three-minute delayed with the targetoid appearance. MR images demonstrate avid enhancement of the right hepatic lesion (white arrows).

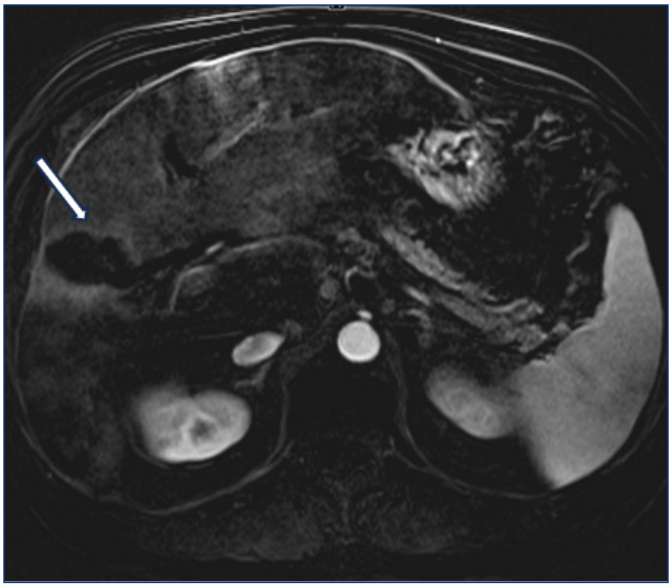


TREATMENT AND OUTCOMES

Surgical resection with curative intent is the mainstay treatment for CCA. However, only 25% of patients have resectable CCA.[41] The National Comprehensive Cancer Network (NCCN) recommends six months adjuvant therapy with capecitabine in patients who underwent surgical resection with negative margins and negative regional nodes.[42] The phase III trial of the BILCAP study demonstrated a significant improvement in overall survival for patients who received eight cycles of capecitabine compared to the control group.[43] The NCCN recommends either durvalumab or pembrolizumab in combination with gemcitabine and cisplatin for patients with unresectable or metastatic disease, as indicated by findings from the phase III TOPAZ-1 and phase III randomized KEYNOTE-966 trials.[42,44,45]

Other treatment options, such as liver transplantation or locoregional therapies can be considered. Liver transplantation, previously contraindicated in pCCA, is another option

Figure 4. Axial T1 post-contrast subtraction MR image demonstrating no enhancement associated with right hepatic lesion (white arrow), one month post-ablation.



for treating CCA. A single-center retrospective study of 216 patients with early-stage unresectable pCCA who received liver transplantation following neoadjuvant chemoradiotherapy demonstrated a five-year disease-free survival of 65% and with an intent-to-treat five-year survival of 53%.[46] Some evidence exists for the use of locoregional therapies, such as radiofrequency ablation, transarterial chemoembolization, and transarterial radioembolization, but these treatment options mainly serve palliative purposes (**Figure 4**).[47,48] Recommendations for use also vary depending on the expert groups.

CONCLUSION

Cholangiocarcinoma (CCA) is a rare and aggressive liver cancer associated with poor outcomes. Over the past couple of decades, the incidence rate of CCA has been rising globally. Specifically, in the United States, this increase in incidence has been observed across different races, sexes, and ethnicities. Because incidence rate and risk factors vary significantly around the world, with rates highest in Southeast Asia, the complex roles of environment, genetics, and socioeconomic status in the pathogenesis of CCA are difficult to elucidate. Regardless, it is challenging to diagnose CCA due to its indolent course. Patients in whom CCA is suspected should undergo appropriate imaging, namely MRI with MRCP or CT, for tumor characterization and staging. Although surgery with curative intent is the gold standard for treating CCA, the prognosis remains poor due to late presentation and high recurrence rate. Adjuvant chemotherapy is recommended post-resection, and for unresectable cases, systemic therapy and other palliative treatment may be considered. Ultimately, CCA is challenging to detect and even more challenging to treat. Given its rising incidence globally, further study of CCA's risk factors, means to achieve earlier diagnosis, and more effective surgical and medical treatment options is paramount.

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